REMARKS

Claims 13-19, 22-25, 28-40, 51-79 are pending in the present application. Claims 1-12, 20-21, and 41-50 have been canceled without prejudice and without acquiescence. Claims 13-9-19, 22-24, 29-32, 36, 40, 51-53, and 57-60 have been amended without prejudice and without acquiescence to clarify the scope of the invention. Claims 26 and 27 are withdrawn. In accordance with 37 C.F.R. 1.141 (a), Applicants will be entitled to consideration of claims 26 and 27 with additional species upon the allowance of a generic claim and as long as the species claims 'are written in dependent form or otherwise include all the limitations of the generic claim'. Claims 62-79 have been added. Support the amendments and new claims can be found in the original claims as filed. Applicants assert that no new matter has been added.

The issues outstanding in this application are as follows:

- Claims 1-25, 28-40 and 48-56 were rejected under 35 U.S.C. § 101 as allegedly lacking unpatentable subject matter.

- Claims 1-25, 28-40 and 48-56 were rejected under 35 U.S.C. § 112, first paragraph.

- Claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 were rejected under 35 U.S.C. § 102 (e) as being anticipated by Palese et al. (US Pat. No. 6022726).

- Claims 1-5, 8, 9, 12-18, 20-24, 29, 33 and 37 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Bergmann et al. (J. General Virology, 1995).

- Claims 1-25 and 28-60 were rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (J. General Virology, 1995); Bergmann et al. (Virus Research, 1996); and Kim et al. (J. General Virology, 1997) in view of Castrucci et al. (J. Virology 1992).

- Claims 1-5, 8-24, 28, 29, 33, 37-39, 48-60 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of US Pat. No. 6022726.

Applicants respectfully traverse the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

I. Rejection under 35 U.S.C. § 101

Claims 1-25, 28-40 and 48-56 are rejected under 35 U.S.C. § 101 as lacking unpatentable subject matter. Applicants respectfully traverse.

While the Applicants continue to disagree with the Examiner and consider that it is untenable that such a mutation would be found in nature, which as previously explained must incorporate a double mutation with a genomic segment, where appropriate, the claims are amended to incorporate the term "isolated." Applicants also note that the claims are now limited to specific mutations at specific positions within the duplex region. This emphasizes the unlikelihood of such mutations occurring in nature.

The Examiner's rejection also seems to be inappropriate taking into account the wording of some of the claims. Not all of the claims are directed to viruses *per se*, but include methods of producing these viruses, *ex vivo* cells infected with such viruses and so on. The Examiner's arguments that the virus itself might occur in nature are clearly irrelevant to claims directed to methods for creating this virus. However, in order to advance the prosecution of the present application, Applicants have amended without acquiescence and without prejudice to indicate that the virus is "isolated."

Since the Examiner agreed during the telephonic interview that this amendment would obviate the rejection, Applicants respectfully request that the rejection be withdrawn.

II. Rejection under 35 U.S.C. § 112

Claims 1-25, 28-40 and 48-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific mutations, does not reasonable provide enablement for predicting the effect of mutations having "functional modifications." Applicants traverse.

In order to advance prosecution of the present application, Applicants have amended the claims without prejudice and without acquiescence to delete the reference to the functional modification. In view of this amendment, Applicants request that the rejection be withdrawn.

III. **Rejection under 35 U.S.C. § 102**

A. Palese et al. (US Pat. No. 6022726)

Claims 1-5, 8-24, 28, 29, 33, 37-39, and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese et al. (US Pat. No. 6022726). Applicants traverse.

In order to advance the prosecution of the present application, Applicants have amended the claims without prejudice and without acquiescence to incorporate the feature that the virus has at least one base pair substitution, the base pair substitution being either at position 11 from the 3' terminus and 12' from the 5' terminus of the native segment, or the base pair substitution being at position 10 from the 3' terminus and position 11' from the 5' terminus of the native segment, which was not rejected under 35 U.S.C. § 102(e). See claim 57.

In view of the amendments, Applicants submit that these claims are not anticipated by Palese et al., US Patent No. 6,022,726. No where in this document is any virus described which includes a base pair mutation either at positions 11/12' or at position 10/11'. The Examiner has objected that the mutation of a base pair does not require the mutation of two nucleotides. In fact, the claim as written refers expressly to a base pair substitution. It is apparent therefore that the claims do not comprise a single mutation, but has a double mutation to lead to substitution of the base pair. In any event, the claims as amended make it apparent that the base pair substitution either includes a mutation at position 11 from the 3' terminus and at position 12' from the 5' terminus or that the duplex region includes mutations at position 10 from 3' terminus and position 11' from the 5' terminus of the native segment. Thus, the claims expressly require a base pair substitution and specifies the two positions at which mutation occurs in order to achieve that desired base pair substitution.

Accordinly, the claims are not anticipated, and Applicants respectfully request that the rejection be withdrawn.

B. Palese et al. (WO 93/21306)

Claims 1-5, 8-24, 28, 29, 33, 37-39, and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese et al. (WO 93/21306). Applicants traverse.

In order to advance the prosecution of the present application, Applicants have amended the claims without prejudice and without acquiescence to incorporate the feature that the virus has at least one base pair substitution, the base pair substitution being either at position 11 from the 3' terminus and 12' from the 5' terminus of the native segment, or the base pair substitution being at position 10 from the 3' terminus and position 11' from the 5' terminus of the native segment, which was not rejected under 35 U.S.C. § 102(e). See claim 57.

Similarly, the claims are not anticipated by Palese WO 93/21306. Applicants note that this document is the International Publication for the PCT application from which US Patent 6,022,726 is derived. The teaching of this document is identical to that of US Patent No. 6,022726. As explained above, this document does not disclose the specific mutations which are now claimed. Furthermore, contrary to the suggestion by the Examiner, the claims clearly do require two mutations to produce a base pair substitution, the positions on the strand relative to the 5' and 3' termini being specified.

Thus, the claims are not anticipated, and Applicants respectfully request that the rejection be withdrawn.

C. Rejection under 35 U.S.C. § 102

Claims 1-5, 8, 9, 12-18, 20-24, 28, 29, 33 and 37 are rejected under 35 U:S.C. 102(b) as being anticipated by Bergmann et al. (J. of General Virology, 1995). Applicants traverse.

In order to advance the prosecution of the present application, Applicants have amended the claims without prejudice and without acquiescence to incorporate the feature that the virus has at least one base pair substitution, the base pair substitution being either at

position 11 from the 3' terminus and 12' from the 5' terminus of the native segment, or the base pair substitution being at position 10 from the 3' terminus and position 11' from the 5' terminus of the native segment, which was not rejected under 35 U.S.C. § 102(e). See claim 57.

Thus, Bergmann et al. does not teach each and every element of the claims and Applicants respectfully request that the rejection be withdrawn.

IV. **Rejection under 35 U.S.C. § 103**

Claims 1-25 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (J. General Virology, 1995); Bergmann et al. (Virus Research, 1996); and Kim et al. (J. General Virology, 1997) in view of Castrucci et al. (J. Virology 1992). Applicants traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The disclosure of Bergman et al., is directed to the production of chimeric viruses. Bergman et al. do not show that base pair substitutions were necessary for attenuation nor does Bergman et al. teach the specific mutations which are now claimed.

The Examiner makes no distinction between a chimeric virus and a mutated virus. However, some distinction must be drawn particularly when considering non-obviousness. If one of skill in the art is taught that a chimera may be useful then that may lead one of skill in the art to produce other chimeras, that is virus made up of two strains. The nature of a chimera is that it effectively combines two portions of known strains together.

In contrast, one of skill in the art considering the provision of a mutated virus is not restricted or limited to selecting portions from two different strains, but has available any level of mutation.

The paper by Bergman et al., does not specify the type of mutation that might be useful in the production of an attenuated virus. While the chimeras of Bergman et al. may

have had a number of base pair mutations, Bergman et al. does not disclose the specific base pair substitutions now claimed nor does Bergman et al. suggests that base pair substitutions were either necessary or sufficient for attenuation. Applicants assert that the present application demonstrates that base pair substitutions at specific positions can be used to cause attenuation.

The Examiner has combined the teaching with Bergman et al., with that of Kim et al., to allegedly produce the present invention. However, Applicants submit that this objection is made with hindsight and fails to properly consider the teaching of either Bergman et al. or Kim et al.

Bergman et al., is specifically concerned with the production of chimeric viruses. It does not provide any teaching relating to individual base pair substitutions nor does it suggest that such substitutions are necessary or sufficient to cause attenuation. Bergman introduces a number of different mutations through the production of chimeras, and it is not possible to establish which mutations are useful.

In more detail, the U6 stretch in the 5' strand is displaced by one nucleotide in NA-Y compared to WSN-WT. Lee and Palese (J. Virol 68: 1245-1249, 1994) show that the position of this polyadenylation signal is important. Poon et al.(J. Virol 73: 3473-3476) also suggest that the position of the U track may explain a lack of mRNA production in a template with the U track displaced by one residue. The 5' terminal strand differs in sequence in NA/Y and WSN-wt. The 3' terminal sequence differs in sequence, not only at the underlined nucleotide sequence in Fig. 1 of Bergman et al., but also in the last 3 nucleotides. The NA/Y sequence is longer than the WSN-wt sequence in its base-paired regions. According to Ortega et al (J.Virol 74: 156-163, 2000), replication efficiency is influenced by the exact number of nucleotides being transcribed (their Fig 6). Therefore changing the length of the transcript might influence the yields of replication intermediates and therefore affect attenuation.

In summary, the attenuation in Bergman et al. could be caused by any number of features that differ in the Bergman viruses compared to the wild types. Bergman does not

make any conclusions relating to the requirement for base pair substitution and certainly does not demonstrate that base pair substitution is necessary and sufficient for attenuation.

Applicants submit that there would be no motivation for one of skill in the art to combine the teaching of Kim et al. which provides specific mutations in the influenza A virus with the chimeras of Bergman et al. If one of the skill in the art is looking to alter Bergman et al. they would look to consider production of other chimeras. There is no reason for one of skill in the art to combine the teaching of Bergman et al. with that of Kim et al. nor is there any expectation of success that combining Bergman et al. with Kim et al. would produce the viruses of the present invention.

Kim et al. reports the studies of base pair mutations in a highly artificial system. No virus was isolated and no attenuation experiments were performed. Thus, Kim et al. does not provide any information on attenuation and does not suggest that the mutations might be useful to achieve attenuation.

Thus, one of skill in the art faced with the teaching of Bergman et al. is only taught that chimeras might be useful to provide attenuated viruses. No further information is provided. Thus, there would be no motivation whatsoever to introduce the mutation such as described in Kim et al. into a wild type virus when seeking to obtain attenuated virus.

Thus, neither Bergmann et al. 1995 nor Bergmann et al. 1996 separately or in combination teach or suggest all of the limitations of the pending claims. Yet further, the addition of Kim et al. and Castrucci et al. do not remedy the deficiencies of either Bergmann 1995 or 1996, thus, Applicants assert that the examiner has not established a *prima facie* case of obviousness, and respectfully request that the rejection be withdrawn.

V. Rejection under Double Patenting

Claims 1-5, 8-24, 28, 29, 33, 37-39, and 48-56 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of US Pat. No. 6022726. Applicants traverse.

Applicants assert that the Examiner has not established a *prima facie* case of obviousness type double patenting.

The fact that claim 1 of US Pat. No. 6022726 mentions an attenuated influenza virus having at least one modified non-coding region in the stem structure does not make obvious the specific modifications that are presently claimed in the pending application. The claims of the pending application have been amended without prejudice and without acquiescence to incorporate the feature that the virus has at least one base pair substitution, the base pair substitution being either at position 11 from the 3' terminus and 12' from the 5' terminus of the native segment, or the base pair substitution being at position 10 from the 3' terminus and position 11' from the 5' terminus of the native segment. This feature is present in original claim 57, which the Examiner has clearly indicated is not present in the US Pat. No. 6022726 because claim 57 was not included in the 35 U.S.C. § 102e rejection. If this feature is novel under § 102, then US Pat. No. 6022726 can not be used to establish a *prima facie* case of obviousness because it is well established that in order to establish a *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Thus, Applicants assert that US Pat. No. 6022726 does not teach or suggest all the limitations of the pending claims.

If the Examiner continues to maintain this rejection, the Examiner must provide clear evidence to establish why an alleged variation of the invention claims in the prior patent would have been obvious. See *In re Kaplan*, 789, F.2d 1574, 229 USPQ 683 (Fed. Cir. 1986). The Examiner has the initial burden to show that the inventions claimed are not patentably distinct based on a *prima facie* showing of obviousness. In view of the above, Applicants assert that this rejection is now moot, and respectfully request that it be withdrawn.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02074US0 from which the undersigned is authorized to draw.

Dated: June 8, 2005

Respectfully submitted,

By _____

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